9-13-00

A

PATENT

Attorney's Docket No.: U 012473-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of Inventors:

1. ANTONIO **LOPEZ CABRERA**
2. PEDRO JUAN **SOLANAS IBARRA**
3. VINCENT **MANCINELLI**

WARNING: *The Declaration must name all of the actual inventor(s).*

For (title):

SOLID ORAL PHARMACEUTICAL FORMULATION OF MODIFIED RELEASE THAT CONTAINS AN ACID LABILE BENZIMIDAZOLE COMPOUND

1. Type of Application

This new application is for a(n) (check one applicable item below):

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date **SEPTEMBER 12, 2000 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL699731472US addressed to the: Assistant Commissioner of Patents, Washington, D.C. 20231**

JENNIFER RASHKIN
(type or print name of person mailing paper)

(Signature of person mailing paper)

NOTE: ***Each paper or fee referred to as enclosed herein has the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 CFR 1.10(b).***

WARNING: ***Certificate of mailing (first class) or facsimile transmission procedures of 37 CFR 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.***

☑ Original (nonprovisional)

☐ Design

☐ Plant

WARNING: ***Do not*** *use this transmittal for a completion in the U.S. of an International Application under 35 U.S.C. 371(c)(4) unless the International Application is being filed as a divisional, continuation or continuation-in-part application.*

WARNING: ***Do not*** *use this transmittal for the filing of a provisional application.*

2. Benefit of Prior U.S. Application(s) (35 U.S.C. 119(e), 120, or 121)

NOTE: *If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, or where the parent case is an International Application which designated the U.S., or benefit of a prior provisional application is claimed, then check the following item and complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.*

WARNING: *If an application claims the benefit of the filing date of an earlier filed application under 35 U.S.C. 120, 121 or 365(c), the 20-year term of that application will be based upon the filing date of the earliest U.S. application that the application makes reference to under 35 U.S.C. 120, 121 or 365(c). (35 U.S.C. 154(a)(2) does not take into account, for the determination of the patent term, any application on which priority is claimed under 35 U.S.C. 119, 365(a) or 365(b).) For a c-i-p application, applicant should review whether any claim in the patent that will issue is supported by an earlier application and, if not, the applicant should consider canceling the reference to the earlier filed application. The term of a patent is not based on a claim-by-claim approach. See Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,205.*

WARNING: *When the last day of pendency of a provisional application falls on a Saturday, Sunday, or Federal holiday within the District of Columbia, any nonprovisional application claiming benefit of the provisional* ***must*** *be filed prior to the Saturday, Sunday or Federal holiday within the District of Columbia. See 37 C.F.R. § 1.78(a)(3).*

☐ The new application being transmitted claims the benefit of prior U.S. application(s) and enclosed are ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

NOTE: If one of the following 3 items apply, then complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED and a NOTIFICATION IN PARENT APPLICATION OF THE FILING OF THIS CONTINUATION APPLICATION.

☐ Divisional.

☐ Continuation.

☐ Continuation-in-Part (C-I-P).

3. Papers Enclosed That Are Required For Filing Date Under 37 CFR 1.53 (Regular) or 37 CFR 1.153 (Design) Application

13 Pages of specification

4 Pages of claims

_1_ Pages of Abstract

_ Sheets of drawing

☐ formal

☐ informal

*WARNING: **DO NOT** submit original drawings. A high quality copy of the drawings should be supplied when filing a patent application. The drawings that are submitted to the Office must be on strong, white, smooth, and non-shiny paper and meet the standards according to § 1.84. If corrections to the drawings are necessary, they should be made to the original drawing and a high-quality copy of the corrected original drawing then submitted to the Office. Only one copy is required or desired. Comments on proposed new 37 CFR 1.84. Notice of March 9, 1988 (1990 O.G. 57-62).*

NOTE: "Identifying indicia, if provided, should include the application number or the title of the invention, inventor's name, docket number (if any), and the name and telephone number of a person to call if the Office is unable to match the drawings to the proper application. This information should be placed on the back of each sheet of drawing a minimum distance of 1.5 cm. (⅝ inch) down from the top of the page." 37 C.F.R. 1.84(c).

(complete the following, if applicable)

☐ The enclosed drawing(s) are photograph(s), and there is also attached a "PETITION TO ACCEPT PHOTOGRAPH(S) AS DRAWING(S)". 37 C.F.R. 1.84(b).

4. Additional papers enclosed

☐ Preliminary Amendment

☐ Information Disclosure Statement (37 CFR 1.98)

☐ Form PTO-1449

☐ Citations

☐ Declaration of Biological Deposit

☐ Submission of "Sequence Listing," computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.

☐ Authorization of Attorney(s) to Accept and Follow Instructions from Representative

☐ Special Comments

☐ Other

5. Declaration or oath

☐ Enclosed

executed by *(check **all** applicable boxes)*

☐ inventors.

☐ legal representative of inventors. 37 CFR 1.42 or 1.43

☐ joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.

☐ This is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. *See item 13 below for fee.*

☑ Not Enclosed.

WARNING: *Where the filing is a completion in the U.S. of an International Application but where a declaration is not available or where the completion of the U.S. application contains subject matter in addition to the International Application the application may be treated as a continuation or continuation-in-part, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION CLAIMED.*

☑ Application is made by a person authorized under 37 CFR 1.41(c) on behalf of *all the above named inventors.* (The declaration or oath, along with the surcharge required by 37 CFR 1.16(e) can be filed subsequently).

NOTE: It is important that all the correct inventor(s) are named for filing under 37 CFR 1.41(c) and 1.53(b).

☐ Showing that the filing is authorized. *(Not required unless called into question. 37 CFR 1.41(d).)*

6. Inventorship Statement

WARNING: *If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.*

The inventorship for all the claims in this application are:

☐ The same

☐ Not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,

7. Language

NOTE: An application including a signed oath or declaration may be filed in a language other than English. A verified English translation of the non-English language application and the processing fee of $130.00 required by 37 CFR 1.17(k) is required to be filed with the application or within such time as may be set by the Office. 37 CFR 1.52(d).

NOTE: A non-English oath or declaration in the form provided or approved by the PTO need not be translated. 37 CFR 1.69(b).

☑ English

☐ non-English

☐ the attached translation is a verified translation. 37 CFR 1.52(d).

8. Assignment

☑ An assignment of the invention to LABORATORIOS DEL DR. ESTEVE, S.A.

☐ is attached. A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

☑ will follow.

NOTE: "If an assignment is submitted with a new application, send two separate letters—one for the application and one for the assignment." Notice of May 4, 1990 (1114 O.G. 77-78).

WARNING: *A newly executed "CERTIFICATE UNDER 37 CFR 3.73(b)" must be filed when a continuation-in-part application is filed by an assignee. Notice of April 30, 1993. 1150 O.G. 62-64.*

9. Certified Copy

Certified copy of application

Country	Appln. No.	Filed
Spain	9902027	September 13, 1999

from which priority is claimed

☐ is attached.

☑ will follow.

NOTE: The foreign application forming the basis for the claim for priority must be referred to in the oath or declaration. 37 CFR 1.55(a) and 1.63.

NOTE: This item is for any foreign priority for which the application being filed directly relates. If any parent U.S. application or International Application from which this application claims benefit under 35 U.S.C. 120 is itself entitled to priority from a prior foreign application then complete item 18 on the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

10. Fee Calculation (37 CFR 1.16)

A. ☑ Regular Application

Claims as Filed							
Number Filed	**Number Extra**					**Rate**	**Basic Fee 37 CFR 1.1-6(a) $690.00**
Total Claims (37 CFR 1.16(c))	24	- 20	=	4	x $	18.00	72.00
Independent Claims (37 CFR 1.16(b))	2	- 3	=	0	x $	78.00	
Multiple dependent claim(s), if any (37 CFR 1.16(d))					+ $	260.00	

☐ Amendment cancelling extra claims enclosed.

☐ Amendment deleting multiple-dependencies enclosed.

☐ Fee for extra claims is not being paid at this time.

NOTE: If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d).

Filing Fee Calculation $

B. ☐ Design application
($310.00 — 37 CFR 1.16(f))

Filing Fee Calculation $

C. ☐ Plant application
($480.00 — 37 CFR 1.16(g))

Filing Fee Calculation $

11. Small Entity Statement(s)

☐ Verified Statement(s) that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is(are) attached or has been filed.

Filing Fee Calculation (50% of **A**, **B** or **C** above) $

NOTE: Any excess of the full fee paid will be refunded if a verified statement and a refund request are filed within 2 months of the date of timely payment of a full fee. 37 CFR 1.28(a).

12. Request for International-Type Search (37 CFR 1.104(d)) *(Complete, if applicable)*

☐ Please prepare an international-type search report for this application at the time when national examination on the merits takes place.

13. Fee Payment Being Made At This Time

☑ Not Enclosed

☑ No filing fee is to be paid at this time. *(This and the surcharge required by 37 CFR 1.16(e) can be paid subsequently.)*

☐ Enclosed

☐ basic filing fee $

☐ Recording assignment
($40.00; 37 CFR 1.21(h)) (See attached "COVER SHEET FOR ASSIGNMENT ACCOMPANYING NEW APPLICATION.")

☐ Petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached. ($130.00; 37 CFR 1.47 and 1.17(h)) $

☐ For processing an application with a specification in a non-English language. ($130.00; 37 CFR 1.52(d) and 1.17(k)) $

☐ Processing and retention fee ($130.00; 37 CFR 1.53(d) and 1.21(l))

☐ Fee for international-type search report ($40.00; 37 CFR 1.21(e)). $

NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 CFR 1.53(d) and this, as well as the changes to 37 CFR 1.53 and 1.78, indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid or the processing and retention fee of §1.21(l) must be paid within 1 year from notification under §53(d).

Total fees enclosed $

14. Method of Payment of Fees

☐ Check in the amount of $

☐ Charge Account No. 12-0425 in the amount of $

A duplicate of this transmittal is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).

15. Authorization to Charge Additional Fees

WARNING: *If no fees are to be paid on filing, the following items should <u>not</u> be completed.*

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.*

☐ The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. 12-0425.

☐ 37 CFR 1.16(a), (f) or (g) (filing fees)

☐ 37 CFR 1.16(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

☐ 37 CFR 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)

☐ 37 CFR 1.17 (application processing fees)

WARNING: *While 37 CFR 1.17(a), (b), (c) and (d) deal with extensions of time under §1.136(a), this authorization should be made only with the knowledge that: "Submission of the appropriate extension fee under 37*

C.F.R. 1.136(a) is to no avail unless a request or petition for extension is filed." (Emphasis added). Notice of November 5,1985 (1060 O.G. 27)

☐ 37 CFR 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311(b))

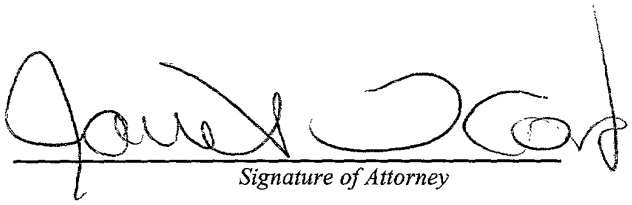
NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b).

NOTE: 37 CFR 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application ... prior to paying, or at the time of paying, ... issue fee". From the wording of 37 CFR 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

16. Instructions As To Overpayment

☐ credit Account No. 12-0425

☐ refund



Signature of Attorney

Reg. No. 33,778

Tel. No. (212) 708-1935

Janet I. Cord
Ladas & Parry
26 West 61 Street
New York, NY 10023

☐ **Incorporation by reference of added pages**

(Check the following item if the application in this transmittal claims the benefit of prior U.S. application(s) (including an international application entering the U.S. stage as a continuation, divisional or C-I-P application) and complete and attach the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED)

☐ Plus Added Pages for New Application Transmittal Where Benefit of Prior U.S. Application(s) Claimed

Number of pages added ___

☐ Plus Added Pages for Papers Referred to in Item 4 Above

Number of pages added ___

☐ Plus "Assignment Cover Letter Accompanying New Application"

Number of pages added ___

☑ **Statement Where No Further Pages Added**

(If no further pages form a part of this Transmittal, then end this Transmittal with this page and check the following item:)

☑ This transmittal ends with this page.

SOLID ORAL PHARMACEUTICAL FORMULATION OF MODIFIED RELEASE THAT CONTAINS AN ACID LABILE BENZIMIDAZOLE COMPOUND

FIELD OF THE INVENTION

The invention relates to new pharmaceutical formulations that contain an acid labile benzimidazole compound, suitable for oral administration, constituted of a number of pellets that comprise the active ingredient, one or more intermediate layers that comprise, at least, a system of modified release, and an external enteric coating. The invention also refers to the procedure for the production of said pellets and pharmaceutical formulations and to the use thereof in Medicine.

BACKGROUND OF THE INVENTION

The compound, 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulphinyl]-1H-benzimidazole, is a benzimidazole compound suitable for inhibiting the gastric secretion in mammals. In particular, it is suitable for the prevention and treatment of disorders related with the secretion of gastric acid, for example, gastric ulcer, duodenal ulcer, reflux esophagitis, Zollinger-Ellison syndrome, etc. Other benzimidazole compounds with anti-ulcer activity are pantoprazole, lansoprazole and rabeprazole.

Omeprazole, just as is the case with other benzimidazole compounds that have therapeutic interest, is an acid labile compound. This causes numerous problems when it comes to developing a pharmaceutical formulation for oral administration due to the fact that when said compound comes into contact with the stomach content, which is a strongly acidic environment, degradation occurs. This lability may be responsible for the variability of the intra- and inter-individual therapeutic response of omeprazole.

To avoid contact between acid labile compounds and gastric juice after oral administration of said compounds, solid pharmaceutical formulations have been developed that comprise a nucleus that contains the acid labile compound and an external layer that constitutes a gastro-resistant coating that may be separated by one or more intermediate layers. In some cases, conventional enteric coatings of acidic nature cannot be used because the active compound would decompose on contact, either direct or indirect, with this coating. This would be evidenced by a colour change and by a reduction in the amount of active compound after a time.

There are several ways of solving the problem related to the stability of the active compound. One of these consists of creating an alkaline environment around the acid labile benzimidazole compound, which is achieved using alkaline salts of the benzimidazole compound and/or incorporating a compound of alkaline reaction in the pharmaceutical gastro-resistant preparation [see, for example, European patent application EP 0 244 380 and the North American patent US 4.786.505]. Another way of solving the problem of stability of the active compound is based on the creation of a physical barrier

that manages a complete separation between the active compound and the enteric layer, thus avoiding any degradation of the active compound, and comprises the use of acceptable pharmaceutical excipients except those that give an alkaline reaction [see, for example, European patent EP 0 773 025].

The European patent application EP 0 244 380 describes pharmaceutical formulations suitable for oral administration of acid labile substances that comprise (a) a nucleus that contains the active substance along with a compound of alkaline reaction, (b) one or several inert intermediate layers that contain the excipients for the tablets that are soluble in water and which disintegrate quickly in water, a polymer forming a film soluble in water optionally along with compounds of alkaline reaction that act as regulators of pH between the nucleus and the external layer, and (c) an external layer consisting of an enteric coating.

The North American Patent U.S. 4.786.505 describes pharmaceutical formulations suitable for oral administration of omeprazole that comprise (a) a nucleus that comprises omeprazole and a compound of alkaline reaction, an alkaline salt of omeprazole and a compound of alkaline reaction, or only an alkaline salt of omeprazole, (b) one or several inert intermediate layers soluble in water or that disintegrate quickly in water, and (c) an external layer consisting of an enteric coating.

The North American Patent U.S. 5.626.875 describes pharmaceutical formulations suitable for the oral administration of acid labile benzimidazole compounds that comprise (a) a nucleus formed of inert granules, the active compound, an inert polymer soluble in water and excipients that do not exhibit alkaline reactions, (b) an inert layer coating the aforementioned nucleus, formed from a polymer soluble in water and non-alkaline excipients, and (c) an external layer consisting of an enteric coating.

Other pharmaceutical formulations of benzimidazole compounds are described in the PCT patent applications: WO 96/01623, which describes a form of dosing comprised of multiple units that contain omeprazole or an alkaline salt thereof, and that is composed of units deployed in the form of layers, individually covered with an enteric coating, that contain the active compound. These units deployed in the form of enterically covered layers are mixed with excipients for tablets that are then compressed together; and WO 96/01624, that describes a form dosing comprised of multiple units similar to that described in the application PCT WO 96/01623 that contains, by way of the active ingredient, an inhibitor of H^+K^+-ATPase [proton pump], labile in acid medium, for example, omeprazole, lansoprazole or pantoprazole.

One problem associated with some pharmaceutical formulations for oral administration of acid labile benzimidazole compounds is related to the plasma half life of the active ingredient. In general, the plasma concentration of omeprazole, administered by

means of hard gelatin capsules that contain omeprazole pellets with enteric coating, is at peak 2 hours after administration, with a gradual tailing off at later times. This leads to large fluctuations in the concentration of the active ingredient in blood and tissues that in turn leads to the need to carry out frequent administrations of the medicament to maintain a suitable therapeutically effective concentration.

As is known, in order that a certain active ingredient can act in a therapeutically effective manner it is necessary to reach a concentration in blood lying within the range known as the "effective concentration". The concentration in blood of the active ingredient at levels greater than the effective concentration tends to increase the incidence of secondary effects, while concentrations below the effective concentration level would result in a weak or null pharmacological response. With a target to obtain an active ingredient blood concentration level lying within the effective concentration range, different solid pharmaceutical formulations have been developed with modified release that allow the release and absorption of the active ingredient to be adjusted with respect to biotransformation thereof and elimination thereof from the organism, thus allowing the secondary effects to be reduced and prolonging the action of the active ingredient. Despite the numerous advantages that solid pharmaceutical formulations of modified release enjoy not many such pharmaceutical formulations have been described for the administration of omeprazole or other acid labile benzimidazole compounds.

The patent application PCT WO 98/52547 describes a pharmaceutical formulation of an active ingredient, for example, an inhibitor of the proton pump such as omeprazole, suitable for oral administration thereof, that comprises a composition for the controlled release of an active ingredient in the gastric environment during a prolonged period of time consisting of microspheres that comprise an active ingredient in the interior nucleus of the microsphere, a layer controlling the rate of release of the active ingredient consisting of a polymer insoluble in water, and an external layer of a bioadhesive agent in the form of a cationic polymer. In general, these formulations act by releasing the active ingredient in the gastric environment during a prolonged period of time and adhesion thereof to the mucus membranes is achieved.

It would therefore be worthwhile to develop new solid oral pharmaceutical formulations of modified release that increase the arsenal of media that allow effective administration of acid labile benzimidazole compounds. However, due to the characteristics of this type of active ingredient, compounds of an acid nature cannot be used as they might lead to the decomposition of the active ingredient.

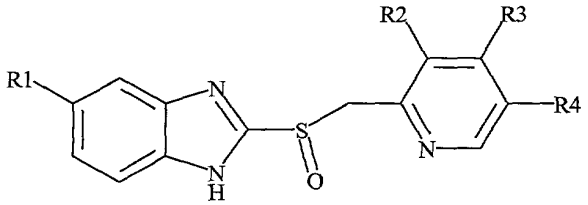
DETAILED DESCRIPTION OF THE INVENTION

The invention provides a solid pharmaceutical formulation of modified release that contains an acid labile benzimidazole compound as an active ingredient, suitable for oral

administration, hereinafter the pharmaceutical formulation of the invention, that comprises a number of pellets that contain the active ingredient, one or more intermediate layers that comprise, at least, a system of sustained release, and an external enteric coating.

In the sense used in this description, the term "acid labile benzimidazole compound" includes the benzimidazole compounds of therapeutic interest whose half life (i) is less than 10 minutes in an aqueous solution that has a pH less than 4, and/or (ii) lies between 10 minutes and 65 hours in an aqueous solution that has a pH of 7, for example, omeprazole, lansoprazole, pantoprazole, rabeprazole, as well as the compounds to which reference was made in the patent application PCT WO 97/12581.

In a particular embodiment, said acid labile benzimidazole compound is a 2[(2-pyridinyl)methylsulphinyl]benzimidazole compound of formula (I)



(I)

where

R^1 is hydrogen, methoxy or difluoromethoxy,

R^2 is methyl or methoxy,

R^3 is methoxy, 2,2,2-trifluoroethoxy or 3-methoxypropoxy, and

R^4 is hydrogen or methyl.

The active pellets, of modified release and gastro-resistant, that contain an acid labile benzimidazole compound as active ingredient, provided by this invention, hereinafter the pellets of the invention, comprise:

an inert nucleus;

an active layer, deposited over said inert nucleus (a), formed by an acid labile benzimidazole compound, an inert polymer, non-alkaline, soluble in water, and one or more pharmaceutically acceptable inert excipients;

one or more intermediate layers that comprise

a non-alkaline inert coating, formed of an inert polymer, non-alkaline, soluble in water and one or more pharmaceutically inert excipients; and

a system of modified release that comprises an inert polymer, non-alkaline, soluble in water and an inert polymer, non-alkaline, insoluble in water;

said intermediate layer or layers being deployed over said active layer (b) that covers the inert nucleus; and

an external layer deployed over said intermediate layer or layers (c) that consists of an enteric coating.

In a particular embodiment, the intermediate layer or layers (c) of the pellets of the invention, contain, separately:

one or more layers that constitute said non-alkaline inert coating; and

one or more layers that contain said system of modified release.

In this particular embodiment said inert coating layers and modified release layers are separated from each other and constitute independent layers. Similarly, the number of layers of inert coating and the number of layers of modified release is variable, as is the order in which these layers appear. They may appear in alternating fashion. In a simple realization, the pellets of the invention included within this particular embodiment comprise a single inert coating layer and a single layer of modified release. A representative example of this particular embodiment of the invention is constituted of some gastro-resistant pellets of modified release, that contain an acid labile benzimidazole compound as active compound, that comprises:

an inert nucleus

an active layer, deposited over said inert nucleus (a), formed by an acid labile benzimidazole compound, an inert polymer, non-alkaline, soluble in water, and one or more pharmaceutically acceptable inert excipients.

(c1) an intermediate layer that constitutes a non-alkaline inert coating deployed over said active layer (b) that covers the inert nucleus, formed from an inert polymer, non-alkaline, soluble in water and one or more pharmaceutically acceptable inert excipients;

(c2) an intermediate layer of modified release, deposited over said inert intermediate layer (c1) that comprises an inert polymer, non-alkaline, soluble in water and an inert polymer, non-alkaline, insoluble in water; and

(d) an external layer deployed over said intermediate layer of modified release (c2) that consists of an enteric coating.

In another particular embodiment, the intermediate layer or layers (c) of the pellets of the invention, contain, mixed among themselves:

said non-alkaline inert coating; and

said system of modified release.

In this particular embodiment said layers of inert coating and modified release are mixed among themselves and constitute a single layer of variable thickness. A representative example of this particular embodiment of the invention is constituted of

some gastro-resistant pellets of modified release, that contain an acid labile benzimidazole compound as active compound, that comprises:

an inert nucleus;

an active layer, deposited over said inert nucleus (a), formed by an acid labile benzimidazole compound, an inert polymer, non-alkaline, soluble in water, and one or more pharmaceutically acceptable inert excipients.

An intermediate layer that comprises (i) an inert non-alkaline coating, soluble in water and one or more inert pharmaceutically acceptable excipients, and (ii) a system of modified release that comprises an inert non-alkaline polymer, soluble in water and an inert non-alkaline polymer, insoluble in water, this intermediate layer being deployed over said active layer (b) that covers the inert nucleus; and

an external layer deployed over said intermediate layer (c) that consists of an enteric coating.

Another particular embodiment contemplated within the scope of the present invention comprises a "mixed" pellet, that is to say, a pellet of the invention in which said intermediate layer or layers (c) comprise a mixture formed by (1) one or more layers of inert coating and one or more layers of modified release, and (2) a mixture consisting of said inert coating and said system of modified release.

The inert nucleus (a) is a pharmaceutically inert substance in relation to the active ingredient, that is to say, it does not react with the active ingredient in the conditions used in such a way that there is decomposition thereof, and it may be composed of a sugar, for example, saccharose, starch and mixtures thereof. In a particular embodiment, said inert nuclei are composed of a mixture of saccharose and corn starch, have an average size lying between 0.3 and 1.4 mm and comply with the requirements of the USP (United States Pharmacopeia) [Monograph of Sugar Spheres, USP NF 18]. In a particular embodiment, the inert nuclei (a) are present in the pellet of the invention in an amount lying between 20% and 70% by weight with respect to the total pellet weight.

The active layer (b) comprises (i) an acid labile benzimidazole compound, preferably a compound of formula (I), more preferably omeprazole, (ii) an inert polymer, soluble in water and non-alkaline, such as hydroxypropylmethylcellulose (HPMC) or hydroxypropylcellulose (HPC) and (iii) one or more pharmaceutically acceptable excipients, such as an anti-tack or diluent, for example, talc. In the sense used in this specification the term "inert", applied to a polymer or an excipient, refers to the fact that said compounds do not react in the conditions used. In a particular embodiment, the active layer (b) is present in the pellet of the invention in an amount lying between 10% and 50% by weight with respect to the total pellet weight.

As has been mentioned earlier, the intermediate layer or layers (c) comprise one or more layers of inert coating and one or more layers of modified release (that is to say, those that contain the modified system of liberation), separated from each other forming one or more intermediate layers or else mixed among themselves forming a single intermediate layer or else a mixed system combining both realizations. In a particular embodiment, the intermediate layer or layers (c) is/are present in an amount lying between 5% and 30% by weight with respect to the total pellet weight.

The layer or layers of inert coating comprise (i) an inert polymer, non-alkaline, soluble in water, such as HPMC or HPC and (ii) one or more inert pharmaceutically acceptable excipients, such as an anti-tack or diluent, for example, talc, and a pigment or opacifier, for example, titanium dioxide.

The layer or layers of modified release comprise(s) a system of modified release that comprises an inert polymer, non-alkaline, insoluble in water, for example ethyl-cellulose (EC) or a copolymer of ammonium methacrylate [Eudragit® RS and RL30D] or any other excipient suitable to modify active ingredient release, along with an inert polymer, non-alkaline, soluble in water such as HPMC, and a plasticizer, for example dibutyl sebacate or similar plasticizers, and an anti-tack agent such as fumed silica or talc. This/these layer(s) provide the retarding character and the modified release of the active compound. The ratio of insoluble polymer:soluble polymer present in this/these layer(s) can vary between very wide limits. Varying the amount of insoluble polymer with respect to the soluble polymer gives a greater or lesser retarding effect [in general, increasing the amount of insoluble polymer with respect to the amount of soluble polymer leads to a slower release of the active ingredient]. In a particular embodiment, the system of modified release is present in the pellet of the invention, typically, in an amount between 5% and 15% with respect to the weight of the pellet.

The external layer (d) deployed over said intermediate layer or layers (c) constitutes the enteric coating and is composed of (i) a gastro-resistant polymer, such as a methacrylate copolymer, for example a copolymer formed by methacrylic acid and esters of methacrylic acid, (ii) a plasticizer, for example, triethyl citrate or similar plasticizers, and (iii) one or more pharmaceutically acceptable inert excipients, for example, talc. In a particular embodiment, the external layer (d) that constitutes the enteric coating is present in the pellet of the invention in an amount lying between 10% and 15% by weight with respect to the total pellet weight.

The pellets of the invention can be obtained by conventional techniques. A review of the different methods for obtaining pellets for pharmaceutical purposes can be found in the book *Pharmaceutical Pelletization Technology,* edited by Isaac Ghebre-Sellassie, Marcel Dekker, Inc., 1989. In a particular embodiment, the pellets of the invention are

obtained applying the different layers by means of conventional fluid bed coating techniques using aqueous solutions or suspensions of the components of such layers. Briefly, in a fluid bed apparatus the inert nuclei are covered with first a layer that contains the acid labile benzimidazole compound, an inert polymer, non-alkaline, soluble in water, such as HPMC or HPC, and one or more inert pharmaceutically acceptable excipients, for example, talc. Then, said active layer is covered with one or more intermediate layers that contain (i) an inert non-alkaline coating, formed by an inert non-alkaline polymer, soluble in water, such as HPMC or HPC, and one or more pharmaceutically acceptable excipients, for example, talc and a pigment or opacifier, such as titanium dioxide; and (ii) a system of modified release that comprises an inert, non-alkaline polymer, soluble in water, such as HPMC, and an inert, non-alkaline polymer, insoluble in water, for example, EC or a copolymer of ammonium methacrylate or any other excipient suitable to modify active ingredient release. This intermediate layer can be formed of a variable number of layers of inert coating and of a variable number of layers of modified release separated, or else it can be formed by a single layer consisting of a mixture of the layers of inert coating and of modified release, or else by a mixture of both types. Finally, the layer of enteric coating is applied which consists of a polymer or copolymer resistant to gastric juice, such as that constituted by methacrylic acid and esters of methacrylic acid, a plasticizer, for example, triethyl citrate, and one or more inert pharmaceutically acceptable excipients, for example, talc.

The pellets of the invention can be administered in an appropriate pharmaceutical formulation, such as a solid pharmaceutical formulation, suitable for oral administration, for example, in the form of hard gelatin capsules or they may be formulated as tablets. The pharmaceutical formulation may contain pellets with different profiles of modified release, that is to say, with systems of modified release that have a differently weighted ratio (insoluble polymer: soluble polymer), for example, they may contain a mixture of (i) pellets with a fast release profile and (ii) pellets with a slow release profile, in a ratio (i):(ii), by weight, lying between 5:95 and 95:5. The pellets with a slow release profile comprise a ratio of insoluble polymer: soluble polymer in the system of modified release greater than in the case for pellets with a fast release profile. In the sense used in this description, the term "pellets with a slow release profile" refers to pellets that release in aqueous medium, pH 6.8, after 30 minutes [that is to say, 150 minutes if the 2 hours in acid medium (HCl) are counted according to Monograph 724 of the USP for "Drug Release", in particular, for Delayed-Release (Enteric coated Articles)] a maximum of 50% of the active ingredient. If the amount of active ingredient released in such conditions is greater than 50% then said pellets are considered, for the purposes of this specification, as

"pellets with a fast release profile". Example 8 shows some illustrative data of pellets with slow release profiles and fast release profiles according to the present invention.

Therefore, the invention provides a solid pharmaceutical formulation of modified release that contains an acid labile benzimidazole compound as active ingredient, suitable for oral administration, that comprises a number of the pellets of the invention, with the same or different release profiles, in a therapeutically effective amount.

The pharmaceutical formulation of the invention can be obtained by conventional methods depending on the exact administration form. A review of the different methods for obtaining pharmaceutical formulations is mentioned in the *Tratado de Farmacia Galénica* (Treatise on Pharmaceutical Formulation), C. Faulí i Trillo, Luzán S, S.A. de Ediciones (1993).

The active ingredients can be administered in the same dose and according to the same protocols as those employed for the existing commercial pharmaceutical formulations. In general, the dose of said active ingredient lies between approximately 1 mg/kg/day and 100 mg/kg/day, adjusted to the individual needs of the patients and according to the criterion of the specialist.

The pharmaceutical formulation of the invention is resistant to being dissolved in acid medium, is stable when passing through the gastric juice and allows the controlled release of the active ingredient in an alkaline or neutral aqueous medium, corresponding to the conditions found in the part near to the small intestine.

The invention also provides a method for the prevention and treatment of disorders related to the abnormal secretion of gastric acid that comprises the administration to the affected patient of a therapeutically effective amount of the pharmaceutical formulation of the invention.

The following examples serve to illustrate the invention. The tests of release of the active ingredient were carried out following the protocol described in Monograph 724 of the USP for "Drug Release", in particular for Delayed-release (Enteric coated Articles)

EXAMPLE 1

A suspension of the active ingredient is prepared by dispersing 80.40 g of active ingredient [omeprazole or lansoprazole], 64.33 g of HPMC and 20.12 g of talc, in 642.86 g of purified water (deionized).

563.03 g of inert, spherical, uniform saccharose nuclei of between 1.0 and 1.2 mm are introduced into a fluid bed apparatus, over which the previously prepared suspension is sprayed. After spraying, and before applying the second layer, the spheres obtained (the inert nuclei covered with the active layer) are dried.

60.54 g of HPMC, 8.04 g of talc and 8.03 g of titanium dioxide are dispersed in 402.86 g of purified water, and the resulting aqueous suspension sprayed over the

previously prepared spheres. After spraying, and before applying the following layer, the spheres thus obtained are dried.

36.20 g of HPMC and 44.25 g of an aqueous dispersion of ethylcellulose (EC) (ratio of EC:HPMC 55:45) are dispersed in 631.43 g of purified water and the resulting aqueous suspension sprayed over the previously obtained spheres. After spraying, and before applying the following layer, the spheres thus obtained are dried.

88.50 g of copolymer of methacrylic acid of USP/Ph.Eur quality (aqueous dispersion type C), 13.28 g of triethyl citrate and 13.28 g of talc are dispersed in 285.71 g of purified water, and the resulting aqueous suspension sprayed over the previously obtained spheres. After applying this layer of enteric coating the resulting spheres (pellets) are dried. The pellets obtained have a slow release profile.

EXAMPLE 2

The procedure described in Example 1 was repeated with the exception that the suspension that contained the components of the intermediate layer of modified release contained 24.14 g of HPMC and 56.31 g of an aqueous dispersion of EC (ratio of EC:HPMC 70:30). The pellets obtained have a very slow release profile.

EXAMPLE 3

A suspension of active ingredient was prepared dispersing 81.79 g of active ingredient [omeprazole or lansoprazole], 62.91 g of HPMC and 19.66 g of talc, in 629.10 g of purified water (deionized).

547.34 g of inert, spherical, uniform saccharose nuclei of between 1.0 and 1.2 mm are introduced into a fluid bed apparatus, over which the previously prepared suspension is sprayed. After spraying, and before applying the second layer, the spheres obtained (the inert nuclei covered with the active layer) are dried.

58.98 g of HPMC, 7.86 g of talc and 7.86 g of titanium dioxide are dispersed in 393.20 g of purified water, and the resulting aqueous suspension sprayed over the previously prepared spheres. After spraying, and before applying the following layer, the spheres thus obtained are dried.

39.32 g of HPMC and 39.32 g of an aqueous dispersion of ethylcellulose (EC) (ratio of EC:HPMC 50:50) are dispersed in 786.40 g of purified water and the resulting aqueous suspension sprayed over the previously obtained spheres. After spraying, and before applying the following layer, the spheres thus obtained are dried.

103.81 g of copolymer of methacrylic acid of USP/Ph.Eur quality (aqueous dispersion type C) [Eudragit® L30D], 15.57 g of triethyl citrate [Eudraflex®] and 15.59 g of talc are dispersed in 332.20 g of purified water, and the resulting aqueous suspension sprayed over the previously obtained spheres. After applying this layer of enteric coating the resulting spheres (pellets) are dried. The pellets obtained have a slow release profile.

EXAMPLE 4

The procedure described in Example 3 was repeated with the exception that the suspension that contained the components of the intermediate layer of modified release contained 31.46 g of HPMC and 47.18 g of an aqueous dispersion of EC (ratio of EC:HPMC 60:40). The pellets obtained have a slow release profile.

EXAMPLE 5

The procedure described in Example 3 was repeated with the exception that the suspension that contained the components of the intermediate layer of modified release contained 23.59 g of HPMC and 55.05 g of an aqueous dispersion of EC (ratio of EC:HPMC 70:30). The pellets obtained have a very slow release profile.

EXAMPLE 6

A suspension of the active ingredient is prepared by dispersing 402 g of active ingredient [omeprazole or lansoprazole], 321.65 g of HPMC and 100.6 g of talc, in 3,214.3 g of purified water (deionized).

2,815.15 g of inert, spherical, uniform saccharose nuclei of between 1.0 and 1.2 mm are introduced into a fluid bed apparatus, over which the previously prepared suspension is sprayed. After spraying, and before applying the second layer, the spheres obtained (the inert nuclei covered with the active layer) are dried.

302.7 g of HPMC, 40.2 g of talc and 40.15 g of titanium dioxide are dispersed in 2,014.3 g of purified water, and the resulting aqueous suspension sprayed over the previously prepared spheres. After spraying, and before applying the following layer, the spheres thus obtained are dried.

162.91 g of HPMC and 957.36 g of an aqueous dispersion of ethylcellulose (EC) (ratio of EC:HPMC 85:15) are dispersed in 3,157.15 g of purified water and the resulting aqueous suspension sprayed over the previously obtained spheres. After spraying, and before applying the following layer, the spheres thus obtained are dried.

1,475 g of copolymer of methacrylic acid of USP/Ph.Eur quality (aqueous dispersion type C) [Eudragit® L30D], 66.4 g of triethyl citrate [Eudraflex®] and 66.4 g of talc are dispersed in 1,428.55 g of purified water, and the resulting aqueous suspension sprayed over the previously obtained spheres. After applying this layer of enteric coating the resulting spheres (pellets) are dried. The pellets obtained have the nucleus and 4 layers (active, inert coating, modified release and enteric) and a very slow release profile.

EXAMPLE 7

A suspension of the active ingredient is prepared by dispersing 402 g of active ingredient [omeprazole or lansoprazole], 321.65 g of HPMC and 100.6 g of talc, in 3,214.3 g of purified water (deionized).

2,815.15 g of inert, spherical, uniform saccharose nuclei of between 1.0 and 1.2 mm were introduced into a fluid bed apparatus, over which the previously prepared suspension was sprayed. After spraying, and before applying the second layer, the spheres obtained (the inert nuclei covered with the active layer) are dried.

465.61 g of HPMC, 40.2 g of talc, 40.15 g of titanium dioxide and 957.36 g of an aqueous dispersion of EC [ratio of EC:HPMC 67:33] are dispersed in 5,171.45 g of purified water, and the resulting aqueous suspension sprayed over the previously prepared spheres. After spraying, and before applying the following layer, the spheres thus obtained are dried.

1,475 g of copolymer of methacrylic acid of USP/Ph.Eur quality (aqueous dispersion type C) [Eudragit® L30D], 66.4 g of triethyl citrate [Eudraflex®] and 66.4 g of talc are dispersed in 1,428.55 g of purified water, and the resulting aqueous suspension sprayed over the previously obtained spheres. After applying this layer of enteric coating the resulting spheres (pellets) are dried. The pellets obtained have the nucleus and 3 layers [active, intermediate (formed by the inert coating and the modified release system) and enteric] and a very slow release profile.

EXAMPLE 8

RELEASE OF THE ACTIVE INGREDIENT

Following the methodology described in the preceding Examples different batches of pellets of omeprazole have been prepared with different systems of modified release changing only the relative quantities of EC and HPMC with the aim of modifying the ratio of EC:HPMC.

The protocol used in the release assay of the active ingredient is described in Monograph 724 of the USP for "Drug Release", in particular for Delayed-Release (Enteric coated Articles). The percentage of omeprazole released at different times in aqueous medium (pH 6.8) was determined after having previously kept the different pellets for 2 hours in HCl medium.

The results obtained are shown in Table 1.

TABLE 1

Percentage of release of Omeprazole from pellets with differing release profiles

Time (minutes)	Pellets with quick release profile [EC:HPMC] = 55:45	Pellets with slow release profile [EC:HPMC] = 70:30
0	0	0
120	0.4	0.8
125	2.6	2
130	34.6	2.8
135	70.8	5.3
140	90.5	11.1
150	92.2	25.9
165	98.3	47.2
185	100	58.2
210	100	73
240	100	80.8

This assay demonstrated how increasing the amount of EC with respect to the amount of HPMC present in the modified release system led to pellets with slower release profiles of the active ingredient.

CLAIMS

1. A pellet comprising an acid labile benzimidazole compound, wherein the pellet comprises:

an inert nucleus;

a layer disposed over said inert nucleus (a), comprising an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients;

one or more intermediate layers that comprise:

an inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; and

a system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert, non-alkaline polymer insoluble in water;

said intermediate layer(s) (c) disposed over said layer (b) that covers the inert nucleus; and

an external layer comprising an enteric coating disposed over said intermediate layer(s) (c).

2. A pellet according to claim 1, in which said intermediate layers (c) comprise one or more layers of an inert, non-alkaline coating and one or more layers of a system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert, non-alkaline polymer insoluble in water.

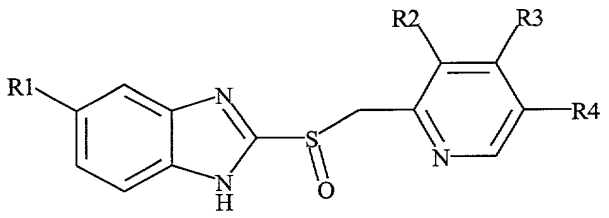
3. A pellet according to claim 1, wherein, the inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients, and the system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert, non-alkaline polymer insoluble in water, are mixed in a single layer.

4. A pellet according to claim 1, in which said intermediate layers (c) comprise a mixture of one or more layers of inert, non-alkaline coating, and one or more layers of said system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert, non-alkaline polymer insoluble in water, and one or more layers of a mixture of inert, non-alkaline coating, and said system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert, non-alkaline polymer insoluble in water.

5. A pellet according to claim 1, wherein the inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients is disposed over the layer (b); the layer comprising the system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert, non-alkaline polymer insoluble in water is disposed over the layer of the inert, non-alkaline

coating; and the layer (d) is disposed over the layer formed by the system of modified release comprising an inert, non-alkaline polymer soluble in water and an inert, non-alkaline polymer insoluble in water.

6. A pellet according to claim 1, wherein said acid labile benzimidazole compound is a compound of formula (I)



(I)

wherein

R^1 is hydrogen, methoxy or difluoromethoxy,

R^2 is methyl or methoxy,

R^3 is methoxy, 2,2,2-trifluoroethoxy or 3-methoxypropoxy, and

R^4 is hydrogen or methyl.

7. A pellet according to claim 1, wherein said acid labile benzimidazole compound is selected from the group consisting of omeprazole, lansoprazole and pantoprazole.

8. A pellet according to claim 1, wherein, said inert, non-alkaline polymer soluble in water, present in the layer (b) is selected from hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC).

9. A pellet according to claim 1, wherein, said inert, non-alkaline polymer soluble in water of the inert, non-alkaline coating, present in the intermediate layer(s) (c) is hydroxypropylmethylcellulose (HPMC).

10. A pellet according to claim 1, wherein, said inert, non-alkaline polymer soluble in water of the system of modified release, present in the intermediate layer(s) (c) is hydroxy-propylmethylcellulose (HPMC).

11. A pellet according to claim 1, wherein, said inert, non-alkaline polymer insoluble in water of the system of modified release, present in the intermediate layer(s) (c) is ethylcellulose or a copolymer of ammonium methacrylate.

12. A pellet according to claim 1, wherein, said external layer (d) comprises a gastro-resistant polymer, a plasticizer and one or more pharmaceutically acceptable inert excipients.

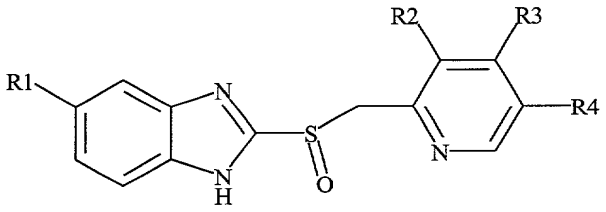
13. A method for obtaining a gastro-resistant pellet of modified release that contains as an active ingredient an acid labile benzimidazole compound, that comprises:

(i) applying an aqueous suspension of an acid labile benzimidazole compound, an inert, non-alkaline polymer soluble in water, and one or more pharmaceutically acceptable inert excipients to cover an inert nucleus;

(ii) applying one or more intermediate layers, separated or mixed among themselves that contain (i) an inert, non-alkaline coating, formed of an inert, non-alkaline polymer soluble in water and one or more pharmaceutically acceptable inert excipients; and (ii) a system of modified release that comprises an inert, non-alkaline polymer soluble in water and an inert, non-alkaline polymer insoluble in water, a plasticizer and an anti-tack agent, separated or mixed; and

(iii) covering said intermediate layer or layers with an aqueous suspension that comprises a gastro-resistant polymer, a plasticizer and one or more pharmaceutically acceptable inert excipients to create an external layer of enteric coating.

14. A method according to claim 13, wherein said acid labile benzimidazole compound is a compound of formula (I)



(I)

wherein

R^1 is hydrogen, methoxy or difluoromethoxy,

R^2 is methyl or methoxy,

R^3 is methoxy, 2,2,2-trifluoroethoxy or 3-methoxypropoxy, and

R^4 is hydrogen or methyl.

15. A method according to claim 13, wherein said acid labile benzimidazole compound is selected from the group consisting of omeprazole, lansoprazole and pantoprazole.

16. A method according to claim 13, wherein, said inert, non-alkaline polymer soluble in water, present in the suspension applied in step (i) is selected from hydroxypropyl-methylcellulose (HPMC) and hydroxypropylcellulose (HPC).

17. A method according to claim 13, wherein, said inert, non-alkaline polymer soluble in water, comprised in the inert, non-alkaline coating, present in the suspension applied in step (ii) is hydroxypropylmethylcellulose (HPMC).

18. A method according to claim 13, wherein, said inert, non-alkaline polymer soluble in water, comprised in the system of modified release, present in the suspension applied in step (ii) is hydroxypropylmethylcellulose (HPMC).

19. A method according to claim 13, wherein, said inert, non-alkaline polymer insoluble in water, comprised in the system of modified release, present in the suspension applied in step (ii) is ethylcellulose or a copolymer of ammonium methacrylate.

20. A composition of modified release that comprises one or more pellets of claim 1.

21. A composition according to claim 20, in which one or more of the pellets have the same release profile of the benzimidazole.

22. A composition according to claim 20, in which one or more of the pellets have a different release profile of the benzimidazole.

23. A composition according to claim 20, comprising a mixture of (i) pellets with a quick release profile and (ii) pellets with a slow release profile, in a ratio (i):(ii), by weight, lying between 10:90 and 90:10.

24. A composition according to claim 20, in the form of a capsule or a tablet.

SUMMARY

SOLID ORAL PHARMACEUTICAL FORMULATION OF MODIFIED RELEASE THAT CONTAINS AN ACID LABILE BENZIMIDAZOLE COMPOUND

The pharmaceutical formulation consists of a number of pellets that comprise an inert nucleus, a layer with the active ingredient, one or more intermediate layers that comprise at least a system of modified release, and an external layer of enteric coating. These pellets can be obtained applying the different layers by means of fluid bed coating techniques using aqueous solutions or suspensions of the components of such layers. The pharmaceutical formulations can be hard gelatin capsules or tablets and are suitable for use in the prevention and treatment of disorders related to abnormal gastric acid secretion.